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**Observational case series study of the long-term efficacy of
Ibogaine-assisted therapy and associated interventions in participants with
opiate addiction treated at the Iboga Therapy House**
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Introduction

This protocol is for an observational case series study of ibogaine-assisted opiate detoxification therapy, a novel pharmacotherapeutic treatment for addiction, and associated interventions. Subjects will be drawn from clients treated independently on a fee-for-services basis at the Iboga Therapy House (<http://www.ibogatherapyhouse.net>) in Vancouver, Canada, where ibogaine is neither a scheduled drug nor the subject of any regulation. The observational study will be conducted by the Multidisciplinary Association for Psychedelic Studies (MAPS) and will enroll 20 individuals treated sequentially for opiate addiction at the Iboga Therapy House. This study is intended to gather preliminary evidence about whether ibogaine-assisted detoxification therapy and associated interventions can lead to changes in problematic opiate use, and facilitate long-term recovery from opiate addiction.

Ibogaine is a naturally occurring psychoactive plant alkaloid with a low potential for abuse. The Iboga Therapy House administers ibogaine hydrochloride, a chemical extracted from the root bark of *Tabernanthe iboga*, a shrub indigenous to West Africa and used in rituals by native populations. It is hypothesized that ibogaine halts or attenuates addiction through two processes, one pharmacological and one psychological. Its pharmacological component relieves the physical symptoms of opiate withdrawal. This is augmented by a psychological component that may be of therapeutic significance to the individual receiving treatment. Clients at Iboga Therapy House receive ibogaine in a supportive setting and receive counseling before and after treatment. The treatment includes the administration of ibogaine and other interventions.

The results of this study may not generalize to treatments of ibogaine-assisted therapy administered in other clinics, or on substances other than opiates. A comparative program analysis of treatments administered at the Iboga Therapy House and the for-profit Ibogaine Association clinic in Mexico (<http://www.ibogaine-therapy.net>) will be conducted by John Harrison for a Psy.D. at the California Institute in Integral Studies.

Baseline data will be gathered prior to treatment at the Iboga Therapy House, with follow-up data gathered for one year, post-treatment. Most follow-up data will be gathered by telephone, since clients of the Iboga Therapy House program come from all over the US and Canada to undergo a five-day residential ibogaine-assisted treatment, and then return home. Data from one or more of the participants' significant others will also be gathered by telephone, as a means of verifying participants' self-reported data. All data will be gathered by Leah Martin, follow-up evaluation coordinator, who has been certified in the administration of the Addiction Severity Index (ASI), the primary outcome variable. Data analysis will be conducted by Lisa Jerome, Ph.D.. Study implementation will be supervised by Kenneth Alper, M.D., who will assist in writing up the results of the study for publication.

Due to the difficulties in verifying the results of voluntary drug testing of participants living all over the United States and Canada, participants' opiate use will not be assessed with drug screens for this case series. In addition, there are problems of uncertain compliance by participants who are not paid to take the drug tests, and the costs of the drug tests themselves are significant. Instead of drug tests, interviews with significant others will be conducted as a means of trying to verify reports of the participants.

Summary of Observational Case Series Study

The Addiction Severity Index (ASI; doc. A) is the primary questionnaire that will be used to determine outcome data within the study. The ASI will be administered at monthly intervals for a period of one year post-treatment to quantitatively measure changes in participants' substance use and lifestyle before and after the ibogaine session, with a focus on opiates. It will be supplemented with additional questions relevant to this particular treatment in the form of participant and clinician surveys. The study coordinator will also be in contact with one or more significant others to try to verify the truthfulness of the participants' information.

Other outcome measures include the Social Identity Questionnaire (SIQ-SR; doc. B), a self-report measure of the degree to which an individual with a substance dependence views him or herself as belonging to a number of pertinent roles, the Peak Experience Profile (doc. C) to gauge the depth of peak and nadir experience (during the ibogaine treatment), the Subjective and Objective Opiate Withdrawal Scales (docs. D and E), and a one to ten-point "pain and craving" rating scale (doc. F).

Participants will be compensated \$10 for each study visit/phone interview they complete, up to a maximum of \$160 for all 16 visits/interviews, to be paid at quarterly intervals throughout the course of the study and in payments valued at up to \$40 per quarterly payment, equaling the form of a gift certificate to a grocery store or restaurant of their choice.

Hypotheses

1. The Iboga Therapy House treatment program will result in changes in substance use, including decreases in average post-treatment scores on the Addiction Severity Index, with scores averaged over a one-year period.
2. The Iboga Therapy House treatment program will result in extended periods of abstinence post-treatment as quantified by average number of days post-treatment without use of opiates, and also by average time to first relapse.

Secondary Hypotheses:

1. Decreases in the Addiction Severity Index post-treatment will be correlated with high scores in both nadir and spiritual experiences as measured by the Peak Experience Profile.
2. The Iboga Therapy House treatment program will result in decreases in the Objective Opiate Withdrawal Scale and Subjective Opiate Withdrawal Scale immediately after treatment.
3. The Iboga Therapy House treatment program will result in extended periods of abstinence and/or extended periods of controlled drug use as quantified by amount of drugs used, and method and schedule of administration relevant to baseline.
4. Average post-treatment scores of Addict Identity measured by the Social Identity Questionnaire-Substance Recovery (SIQ-SR) will be lower than pre-treatment scores.
5. Average post-treatment scores of Work, Recovery, Family and Religious Identity measured by the SIQ-SR will be higher than pre-treatment scores.

Background

Ibogaine: History, Pharmacology, and Use in Treating Chemical Dependence

Ibogaine is a naturally occurring indole alkaloid obtained from the root bark of the shrub *Tabernanthe Iboga* with a history of use as a medicinal and ceremonial agent in West Central Africa and a complex pharmacological profile. It has been alleged to be effective in the treatment of chemical/substance dependence (Alper 2001). Lotsof first described the effects of ibogaine upon heroin dependence in 1962. However, the US placed ibogaine in the most restrictive drug class, Schedule 1, in 1967. Lotsof obtained a use patent for ibogaine therapy in 1986 and formed a private company to develop ibogaine as a treatment for chemical dependence (Alper 2001). Evidence for ibogaine's effectiveness includes a substantial preclinical literature on reduced drug self-administration and withdrawal in animals and case reports in humans (Alper et al. 2001). The National Institute on Drug Abuse (NIDA) has given significant support to animal research, but has rejected grant applications to study ibogaine in humans. The U.S. Food and Drug Administration (FDA) has approved a Phase I dose escalation study in humans in 1993 which has not been completed due to lack of funding (Alper et al. 2001). There is relatively little financial incentive for the development of ibogaine by the pharmaceutical industry because it is isolated from a botanical source in which it naturally occurs, and its chemical structure cannot be patented. This has left the academic community and the non-profit sector with a crucial role in research on ibogaine.

Pharmacological effects of ibogaine include antagonism at NMDA and mu opioid receptors and possible alteration of secondary messenger systems that regulate opioid receptors (Alper 2001; Popik and Skolnick 1999; Sweetnam et al. 1995), and actions on the serotonin and dopamine systems as well. Studies in rodents confirmed that ibogaine reduced or eliminated signs of opiate withdrawal and drug self-administration (Alper et al. 2001, see for example Dworkin et al. 1995; Glick et al. 1992). It has a low potential for abuse and has been demonstrated to be useful as a novel pharmacotherapeutic detoxification method for chemical dependence through a single administration modality. It halts or attenuates chemical dependence through direct pharmacological effects on withdrawal symptoms and reduction in self-administration, and through producing subjective effects that serve as a psychotherapeutic adjunct. Ibogaine has been termed an oneirophrenic; a substance that elicits 'a dream phenomenon without loss of consciousness or change in the perception of the environment or any illusions or formal deterioration of thought and without depersonalization' (Goutarel et al 1993).

Ibogaine side effects include ataxia (loss of muscle coordination), tremors, photosensitivity (sensitivity to light), nausea, vomiting and slight changes in blood pressure (Mash et al. 1998; Alper 2001). These effects subside 24-48 hours after ingestion. Risks associated with therapeutic doses of ibogaine include changes in blood pressure or pulse, dehydration due to vomiting, heart arrhythmias, potentiation of opiates and stimulants, and possible interaction with drugs metabolized via the CYP4502D6 pathway. There have been eight reported fatalities after ibogaine treatment (Alper 2001; DeRienzo and Beal 1997¹; Cearley and Crabtree 2006). In the autopsies performed after these eight deaths, it was found that cause of death in five of the cases was inconclusive or not specifically attributed to ibogaine or ibogaine toxicity. All of these deaths may have been avoided with proper screening.

Researchers in the Netherlands and elsewhere in Europe began using ibogaine treatments to reduce or overcome chemical dependence, with treatments often occurring in non-conventional medical settings (Alper et al. 2001). Ibogaine treatment providers have included "underground" peer-to-peer networks, both in quasi-medical and medical settings. People have formed a number of ibogaine treatment clinics or centers in places where the compound remains unscheduled, such as Mexico, Canada, and the Caribbean island of St. Kitts and Europe. People seeking ibogaine treatment are generally self-referred and hear about ibogaine through friends, the media or through searching the internet. In general, most claim that they have lost faith in current standard models of treatment programs or 12 step models that are solely abstinence focused and/or religiously based, or they wish to halt methadone dependence for which no effective treatment is available other than the time-consuming and often

¹ "Ibogaine Fatalities," accessed on-line at <http://www.myeboga.com/fatalities.html> March 13, 2006.

physically painful method of tapering doses down until they are no longer dependent.

Despite the potential for serious adverse effects, including death, and the lack of controlled studies of long-term effects, people continue to seek out ibogaine to treat their addictions, sometimes traveling across a continent or to another country in order to undergo ibogaine treatment. Given the continued demand for ibogaine treatment, it is important to learn more about the long-term effects of this substance-based therapy.

Evidence of Efficacy of Ibogaine in Humans

Only a few case series and qualitative examinations have addressed the efficacy of ibogaine as a treatment for chemical dependency (Alper et al. 1999; Lotsof 1995; Mash et al. 2001), and there have been no systematic studies examining long-term efficacy of the treatment in reducing or eliminating problem substance use.

Opioid dependence is the most common indication for which addicts have sought ibogaine treatment, and it has typically been administered as a single dose. Commonly reported features of case reports describing ibogaine treatment (Sisko 1993; Mash et al 1998; Cantor 1990; Luciano 1998; Luciano et al. 2000) are reductions in drug craving and opiate withdrawal signs and symptoms within 1 to 2 hours of ibogaine administration, and sustained, complete resolution of the opioid withdrawal syndrome after the ingestion of ibogaine. These case studies appear consistent with general descriptions of ibogaine treatment (Lotsof, 1995; DeRienzo & Beal 1997; Kaplan 1993).

Alper et al. (1999) summarized 33 cases treated for the indication of opioid detoxification in nonmedical settings under open label conditions. These cases are a subset of those presented at the NIDA Ibogaine Review Meeting held in March, 1995, focusing on symptoms of acute opiate withdrawal. The participants in this series of cases reported an average daily use of heroin of 0.64 ± 0.50 g, primarily by the intravenous route, and received an average dose of ibogaine of 19.3 ± 6.9 mg/kg (range of 6 to 29 mg/kg). Resolution of the signs of opioid withdrawal without further drug seeking behavior was observed in 25 participants. Other outcomes included drug-seeking behavior without withdrawal signs (four participants), drug abstinence with attenuated withdrawal signs (two participants), drug seeking behavior with continued withdrawal signs (one participant), and one fatality, possibly involving surreptitious heroin use.

Mash et al. (2001) reports having treated more than 150 participants for substance dependence in a clinic located in St. Kitts, West Indies. A subset of 32 of these participants was treated with a fixed dose of ibogaine of 800 mg for the indication of opioid withdrawal. Physician ratings utilizing structured instruments

for signs and symptoms of opioid withdrawal indicated resolution of withdrawal signs and symptoms at time points corresponding to 12 hours following ibogaine administration and 24 hours after the last use of opiates, and at 24 hours following ibogaine administration and 36 hours after the last use of opiates. Mash and colleagues found that resolution of withdrawal signs and symptoms was sustained during subsequent observations over an interval of approximately one week following ibogaine administration. Depression scores and craving remained significantly reduced one month after treatment (Mash et al. 2000). The authors noted that ibogaine appeared to be equally efficacious in achieving detoxification from either methadone or heroin. The reported efficacy of ibogaine for the opioid withdrawal syndrome observed in the St. Kitts facility appears to confirm the earlier impressions of the case study literature (Alper, 1999; DeRienzo and Beal, 1997; Lotsof, 1995; Sisko, 1993; Mash, 1998; Canto, 1990; Luciano, 1998; Luciano, 2000; Kaplan, 1993)

Assessing Long-Term Outcome

Treatments of chemical dependencies aim to produce long-term changes in problem substance use. It is important to demonstrate that even short-term interventions produce behavioral changes that outlast the duration of the intervention. Relatively short-term psychotherapeutic interventions often examine outcome at least three months after the intervention (McKay et al. 2005; Ness and Oei 2005). It is recognized that rates of abstinence or problem use increase over time, so examining outcomes over time is a more stringent test of a given treatment for chemical dependencies. Ness and Oei found that attending group cognitive behavioral therapy sessions over time in people with alcohol dependence did not predict improved drinking behavior three months later (Ness and Oei 2005). The addition of telephone counseling to standard intensive treatments for people with alcohol or cocaine dependence improved outcomes 24 months later (McKay et al. 2005), as measured via increased positive urine samples. Ibogaine therapy involves even fewer therapy sessions, and so evaluating long-term outcome is especially important, and finding continued abstinence or reduced opiate use after this intervention could point to alternative, and potentially less time-consuming, substance use treatments.

There is very little data regarding the long-term outcomes (over two weeks post-treatment) in participants treated with ibogaine. Lotsof (1995) presented a summary of 41 individuals treated between 1962 and 1993 at the NIDA Ibogaine Review Meeting held in March 1995. The data consisted of self-reports obtained retrospectively that are essentially anecdotal, but which apparently represent the only formal presentation of a systematic attempt to determine long-term outcomes in participants treated with ibogaine. Thirty-eight of the 41 individuals presented in the summary reported some opioid use, with approximately 10 of these apparently additionally dependent on other drugs, mainly cocaine, alcohol, or sedative-hypnotics, but not tobacco or cannabis. Across the sample of 41 individuals, nine individuals were treated twice and one was treated three times

for a total of 52 treatments. Lotsof recorded the interval of time following treatment during which participants reported cessation of use of the drug or drugs on which they were dependent. Fifteen (29%) of the treatments were reportedly followed by cessation of drug use for less than 2 months, 15 (29%) for at least 2 months and less than 6 months, 7 (13%) for at least 6 months and less than one year, 10 (19%) for a period of greater than one year, and in 5 (10%) outcomes could not be determined.

The proposed observational case series study will be the first to systematically examine the long-term effects of ibogaine treatment and associated interventions offered at the Iboga Therapy House as a treatment for opiate dependence. The study will assess changes in substance use over a 12-month period.

Study Design

The proposed study will consist of one year of follow-up data from twenty participants who are treated for opiate dependency at the Iboga Therapy House facility. This data will be gathered by co-investigator Leah Martin. In order to get a representative sample, we will include data from 20 consecutive clients treated for opiate dependence at the facility who meet all outcome study inclusion criteria without meeting any outcome study exclusion criteria, and who give consent to participate in the observational case series study. All identifying information about the participants such as name, address, or social security numbers will be removed from the data collected for this study. Each participant will be assigned a number by which they will be identified for the purposes of this observational study. Case series data will be compiled and analyzed by Lisa Jerome, Ph.D., who will not have access to any identifying information about the participants.

The Iboga Therapy House (ITH) project was initiated in November of 2002 in Vancouver BC and established in 2003 as a community-based, public health centered option for reducing substance-related harm resulting from habitual and/or problematic use. The program treated a total of 31 people from January 2003 to June 2004, when it closed for lack of operational funding. Preliminary anecdotal results obtained from this period were promising, suggesting a need for further data collection. Currently, ITH is a project of the Iboga Therapy Society, which registered as a non-profit society in British Columbia in May 2005, and is providing ibogaine-assisted detoxification therapy on a non-profit, fee-for-service basis. Ibogaine treatment for chemical dependencies at ITH is based on a holistic harm reduction and health promotion-based approach to recovery and personal exploration, and aims to provide an alternative pharmacotherapy that is neither substitution nor replacement therapy. ITH provides a safe, comfortable and supportive environment intended to maximize the potential benefits of an ibogaine experience and associated interventions and minimize potential risks.

ITH facilities include rooms where clients reside during their stay, a working kitchen, and communal space where people may undertake activities such as yoga, stretching or visual arts. There are ten facilitators on staff with a wide range of skills to monitor and support the clients in their treatment. Two staff members are professional substance use counselors, and there are also a host of community volunteers offering aftercare services. One of two emergency medical technicians (EMTs), 1st Aid Level 3, is available on-site during each ibogaine session in case of an emergency.

The Iboga Therapy House accepts men and women aged 18 or older diagnosed with chemical dependencies. Applicants must indicate that they have sought out and undergone other treatments for their dependencies prior to ITH. Prior to treatment at ITH, applicants must undergo a thorough physical examination through their family doctor or physician and provide test results from an electrocardiogram (ECG), a cell blood count (CBC) with differential and a liver panel (AST/ALT), and all test results must be within normal ranges to be accepted for treatment at ITH.

The treatment program consists of a 5 to 7-day residential program, which includes monitoring before the ibogaine administration, preparation for the experience, a test dose to rule out allergic or toxic reaction, and following a successful outcome of the test dose, an ibogaine administration, monitoring of effects, which may last up to 24-36 hours following ingestion of ibogaine, rest and post-ibogaine integrative work. During the ibogaine therapy session, each client receives a dose of ibogaine hydrochloride (HCl) in the 16-20 mg/kg range administered in capsule form. Facilitators provide support continuously throughout the experience. Following the 24 to 36 hour ibogaine experience, and after the client has had some rest and food, ibogaine-assisted therapy returns to the more commonly used model of therapeutic integrative work, and the facilitators or therapist actively work with clients to help process the material experienced through ibogaine's subjective psychological effects. The remainder of the stay is focused on rest and integration. Clients may engage in activities such as light stretching, yoga, soothing baths or walks, and other therapeutic activities such as creating art relating to the experience. The substance use counselor on staff facilitates discussion of the client's experience and works with the client to integrate healthy factors into the client's life in various ways through goal setting and lifestyle changes. It is understood that taking the time to reflect on the Ibogaine experience is a necessary part of the healing process after this mode of therapy.

This observational study of the long-term effects of ibogaine treatment and associated interventions will meet scientific and ethical standards for human experimentation when approved by IRB Services. However, the ibogaine treatment itself, which is legal in Canada and offered by the Iboga Therapy House on a fee-for-services basis, has not been submitted to either Health Canada or an IRB for approval. As a result, the ITH's ibogaine treatment itself

cannot be assumed to have met the scientific and ethical standards for human experimentation.

Inclusion Criteria

1. Participation in this study must be voluntary and not coerced.
2. Participants must be diagnosed with a primary dependency on opiates.
3. Participants must already be planning to undertake ibogaine therapy at Iboga Therapy House and must meet all medical and psychiatric criteria required for receiving ibogaine treatment through their program.
4. Participants must be fluent in English, and they must be able to speak, understand, read, and write in English.
5. Participants must be able to provide at least one significant other (therapists, counselors, parents, spouses, close friends) who can be contacted by the research team to verify information.

Exclusion Criteria

1. Persons receiving ibogaine for any reason other than opiate dependence.
2. Persons who have been treated with ibogaine in the past for any reason.

Outcome Measures

Outcome measures were chosen to be reliable, well-validated, and repeatable. Special consideration was given to measures that assess several indicators of treatment success in addition to abstinence.

The Addiction Severity Index Lite (ASI; doc A) is the primary outcome measure that will be used to assess changes in the participants' lives before and after the ibogaine treatments. It is an assessment instrument designed to be administered as a semi-structured interview in one hour or less. An overall composite score of addiction severity can be derived from the participants' responses during this interview. This score will be our primary measure of this variable. This score is derived from seven sub-scale scores: employment status, medical status, psychiatric status, family/social status, alcohol use, drug use, and legal status. A baseline score will be derived from an in-person interview pre-treatment with the study outcome coordinator. Subsequent outcome scores will be derived from either in-person or telephone interviews using the ASI follow-up revision. The study outcome coordinator has received formal training in the administration and scoring of the ASI.

The Peak Experience Profile (PEP; doc C) measures the highs and lows of a psychedelic experience. It will be the primary measure of the intensity and completeness of the subjective psychological experience of the ibogaine session. Participants will complete the PEP on paper. It is supplemented by a brief written or voice-recorded subjective explanation of the experience.

The Social Identity Questionnaire (SIQ-SR; doc B) will be administered to track changes in identity over the course of the study. It measures five different types of identities: addict, work, recovery, family, and religious. These identities may change as a former addict takes on a new lifestyle and begins to see him or herself as a person with new values and interests.

The Subjective Opiate Withdrawal Scale (SOWS; doc F) is a self-reported survey of opiate withdrawal symptoms. The Objective Opiate Withdrawal Scale (OOWS; doc G) is a therapist-rated survey of visible physical opiate withdrawal symptoms. These two instruments will be administered to participants before and immediately following treatment to measure whether opiate withdrawal symptoms are attenuated after the ibogaine session. The SOWS is also administered once a week for a period of two weeks after the participant has left the facility.

Pain and craving are measured with a ten-point Pain and Craving Survey (doc H) before and after treatment. The pain questions account for cases in which opiate addiction was an attempt at self-medication for chronic pain, or cases in which cessation of opiate use reveals underlying pain and the influence of pain on treatment outcomes. It is either administered on paper during face-to-face interviews, or over the telephone, with the interviewer recording the participant's responses.

Participants are required to provide the outcome coordinator with contact information for at least one significant other (therapists, counselors, parents, spouses, close friends). The outcome coordinator will contact the significant other(s) to independently verify information regarding the participants' substance use both as part of screening and during the one-year follow-up period. Significant other(s) will also help to keep track of participants who may otherwise be lost to follow up.

Valerie Mojeiko (Clinical Research Associate for MAPS) and members of the research team designed supplementary surveys to address aspects of outcome specific to this form of therapy that are not included on the ASI, and to provide additional information for the Iboga Therapy House to use in updating their procedures. At each point of follow-up contact after leaving the facility, the participants will be asked to reflect on their ibogaine session and recovery in a short survey (Participant Questionnaire; doc I). The follow-up interviewer is also asked a short set of questions (Follow-up Interviewer Questionnaire; doc J) that include rating the degree of possible benefit the participants might receive from another ibogaine treatment, with ratings made on a five-point Likert scale. Other items are open-ended questions concerning the health, life and drug use behavior of the participant. Information gathered from these surveys will not be examined in this study but may be examined at a later time. See Appendix A for the surveys.

Schedule of Outcome Measures

Time: w=week m=month	I n t a k e	P o s t	W 1	W 2	W 4/ M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 1 0	M 1 1	M 1 2
ASI	X				X	X	X	X	X	X	X	X	X	X	X	X
PEP		X														
Brief Desc.		X														
Discharge		X														
SIQ-SR	X						X			X			X			X
SOWS	X	X	X	X												
OOWS	X	X														
Pain/ Craving	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
S.O. Check			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Part. Quest.			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interviewer Q			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures

This observational case series study consists of sixteen assessments, including two made immediately before and after ibogaine treatment, two weekly assessments made for the first two weeks after completion of ibogaine treatment, and monthly assessments continuing for 12 months after initial ibogaine treatment. Assessments made immediately prior to and after ibogaine treatment will occur at Iboga Therapy House, while all other assessments will either be conducted in person at ITH or over the telephone. Assessment instruments and sessions are designed to be as unobtrusive as possible, while still gathering data crucial to determining the effect of ITH treatment on opiate addiction.

Upon arrival at ITH, individuals undergo intake and screening by ITH staff to establish that they can safely receive ibogaine treatment (as described in detail on p. 10 of this protocol). Clients at ITH must either demonstrate that they meet criteria for receiving ibogaine or must have a documented medical examination that can be used to assess whether or not they meet study criteria. The observational study outcome coordinator will approach each prospective participant after he or she has elected to undergo ibogaine treatment, but at least 24 hours prior to the administration of ibogaine, and will enroll the first 20 clients with opiates as their primary dependency who consent to take part in the study.

The outcome coordinator will provide prospective participants with consent materials for the study, explaining to them that participation in the study is not a required part of ibogaine treatment. She will discuss the nature of the study with each participant and answer any questions prior to obtaining consent.

If the participant consents to take part in the observational study and meets all inclusion criteria without meeting any exclusion criteria, the participant will complete the ASI, SIQ-SR, Pain and Craving Surveys and the SOWS prior to receiving ibogaine treatment. The ITH staff member performing intake or the counselor monitoring the participant prior to and during ibogaine treatment will complete the OOWS at this time.

All participants will undergo ibogaine treatment under the conditions described on pp. 9-10 of this protocol. They will not complete any observational study-related measures during the course of ibogaine treatment. ITH staff will monitor the participant throughout the period of drug effects.

After all drug effects have subsided, participants will write a brief narrative description of what they experienced during ibogaine treatment, and they will complete the Peak Experience Profile (PEP). They will also complete the Pain and Craving survey and the SOWS. At this point in time, participants will provide the outcome coordinator with contact information for themselves and for the significant other(s) who will serve as means of verifying information they provide about drug use behaviors. The outcome coordinator will store all personal information separately from outcome measures or study related material.

The observational study outcome coordinator will contact the participant and his or her designated significant other(s) one and two weeks after discharge from ITH. She will administer the Pain and Craving survey, the SOWS, and Participant Questionnaire either in person or over the telephone. The outcome coordinator will verify the participant's self-reported information with his or her designated significant other or significant others. After assessing the participant, the outcome coordinator will complete the "Interviewer Questionnaire," providing her impressions of and beliefs about the success of ibogaine treatment and associated interventions in altering substance use related behaviors, with a focus on opiates. The outcome coordinator will make eight attempts to reach the participant, weekly for the first two weeks and twice weekly for the next four weeks, after which the participant will be considered relapsed.

The observational study outcome coordinator will administer all outcome measures save the SIQ-SR to the participant and designated significant others on a monthly basis for the next 12 months. Participants will complete the SIQ-SR three, six, nine and 12 months after receiving ibogaine treatment and associated interventions. The SIQ-SR will either be completed via face-to-face contact with the study's outcome coordinator or over the telephone. The observational study outcome coordinator may administer outcome measures in person or over the telephone to the participant and his or her designated significant others. She will continue to complete the Interviewer Questionnaire for each monthly period. The outcome coordinator will indicate that a participant has relapsed if she cannot reach the participant within six weeks of the previous contact.

If the participant seeks and undergoes another ibogaine treatment session, they will write another short narrative description of their experience during ibogaine treatment program and complete the PEP again. Monthly assessments will continue until a year has elapsed since the initial ibogaine treatment.

The participant will receive the agreed-upon compensation three, six, nine and 12 months after enrolling in the case study.

Each participant will be deemed to have completed the study after one year of interviews and assessments by the observational study outcome coordinator. If a participant is lost to follow-up before a year has elapsed from initial ibogaine treatment, the participant will be considered relapsed, but his or her data will be retained. There will be no replacements of participants lost to follow-up.

The study's outcome coordinator will store and maintain records of all outcome assessments in a locked file cabinet. She will enter study data into an electronic format, using only the participant's assigned subject number. No personal or identifying information will be stored electronically alongside outcome measures used for analyses. Data analysis will be conducted by following the plans described below in "Data Collection and Analysis".

Risks of Study Participation

Participants do not face any foreseeable physical risks from taking part in this observational case series study, which is designed to be as unobtrusive as possible so as not to alter or affect the course of treatment offered by ITH. Chief risks of study participation include psychological distress and risks related to discussing sensitive information, including potentially illegal activities.

The observational study outcome coordinator will be speaking with participants about their mood, life experiences and the degree to which they are following their recovery plan. They will also be discussing relationships and other social roles and the ways in which their substance use and dependence has affected their lives. These interviews and measures may make participants more anxious, angry, sad or disappointed, and discussing any instances where they did not follow their recovery plans may also make them upset. Psychological distress is an unavoidable possibility of conducting the interviews and administering outcome measures. If participants do experience distress while talking with the outcome coordinator, the coordinator may encourage them to seek a psychotherapist or to join a support group.

Participants will be discussing sensitive information concerning their substance use behavior, including personal information about work and family relationships and potential discussion of potentially illegal activities. Discussing and recording sensitive information is an unavoidable aspect of participating in

this observational study. Because of the risks posed by breach of confidence in this study, the researchers will ensure that this information will never be associated with the participant's name. Once a participant consents to take part in the study, the researchers will create an information file and assign the person a case number, and they will keep this information separate from the participant's name. The researchers will store all information in a locked file cabinet. Outcome measures will not be marked with the participant's name.

Data Collection and Analysis

The observational study outcome coordinator will track any instances of relapse or recovery during the twelve-month period covered by this study. A participant will be considered to have relapsed if he or she cannot be reached for follow-up after six weeks have elapsed from the previous contact without subsequent communication, or if he or she reports returning to opiate use. A participant will also be considered relapsed if a significant other reports more than one sign of opiate use, or witnessing actual opiate use. The outcome coordinator will attempt to distinguish between relapses that involve uncontrolled use and relapses that involve controlled use.

Sub-scale and total scale scores will be computed for each outcome measure at each time point, including ASI, the PEP nadir and spiritual experience scales, SIQ-SR scores of addict, work, recovery, family and religious identities, and both the SOWS and OOWS.

All outcome measure scores at baseline will be compared with post-treatment scores except for PEP scores, since this measure will only be administered once after ibogaine treatment. ASI, and SIQ-SR scores will be averaged across the twelve-month period of the study. OOWS and SOWS scores will be averaged across the two-week period when participants are assessed for signs of withdrawal. If data is missing for one point in time, this data will be replaced with the individual's average score across all other points in time. If there are scores missing for more than one point in assessment, then averages will be calculated for the period of time when data was collected. If it is found that none of the participants maintain contact with the outcome coordinator for twelve months, then analyses will instead be based on the longest period for which data has been collected for a given participant.

Secondary analyses (described below) will be performed to compare people who have received one ibogaine treatment with people who have returned to the Iboga Therapy House for subsequent ibogaine treatments.

A. Descriptive Statistics

Period of abstinence will be assessed through several means. Data will be collected concerning self-reported abstinence or relapse at each point during the

follow-up. The significant others' beliefs concerning the participants' abstinence will also be collected at each point during follow-up as a means of verifying self-reported abstinence. Participants whose self-reports of abstinence are verified by others' reports will be considered abstinent at each data collection point. Self-reported relapse, significant others' report of relapse, or failure to maintain contact for six weeks, as described above, will be considered indications of relapse. Period of abstinence will be considered all time points when the participant is abstinent, as reported by the self and significant others.

An instance of use of opiates will be scored as an instance of controlled use if the report given by the participant and at least one significant other agree that the use is controlled. Days of controlled use will be coded across all data collection points, and these will be used to calculate an average period of controlled use for the sample. A separate calculation of the average periods of time post-treatment without uncontrolled use will also be performed. Separate calculations will be performed for participants who received one ibogaine treatment and participants receiving subsequent ibogaine sessions.

Period of abstinence will be measured as above for all participants and averaged across the sample. Separate averages will also be calculated for people who received one ibogaine-assisted session and for people who received more than one session. Separate analyses will also compare abstinence and controlled use in problem substances other than opiates.

B. Primary Analyses

A repeated-measures analysis of variance (ANOVA) will be performed to compare baseline ASI scores with average post-treatment ASI scores. Time of data collection (baseline versus average post-treatment) will serve as a repeated measure. It is predicted that average post-treatment ASI scores will be lower than pre-treatment scores. Because of the exploratory nature of this study and in recognition of potential fluctuations in response over time, secondary analyses (described below) will be performed to look for patterns that might be missed by looking only at average scores.

Repeated measures analyses of variance will be used to compare baseline SIQ-SR, OOWS and SOWS scores with average post-treatment SIQ-SR, OOWS and SOWS scores, with time of data collection (baseline versus post-treatment average) serving as the repeated measure. As described above, secondary analyses examining differences across all data collection points will be performed.

C. Secondary Analyses

In order to more definitively assess long-term effects of the Iboga Therapy house treatment program, we will calculate two averages for post-ibogaine

treatment ASI, Pain-Craving, Participant and Significant Other questionnaire scores. One average will include measures administered from one week to one month after ibogaine treatment, and the second average will include scores obtained from two months to 12 months post-treatment. A repeated-measures ANOVA will be performed on pre-ibogaine scales and the two post-ibogaine time-points. It is predicted that decreases in ASI scores, average number of days without opiate use will occur both one month after undergoing ibogaine treatment and associated interventions and two to 12 months later.

A correlational analysis will also be performed to examine the relationship between PEP nadir and spiritual experience scores and average post-ibogaine ASI scores. It is predicted that post-ibogaine average scores will be positively correlated with both spiritual experience and nadir scores.

If two or more participants receive subsequent ibogaine-assisted sessions during the course of the follow-up, then the analyses comparing baseline and average post-ibogaine scores described above will also be compared across groups through a between-participants (one versus more than one ibogaine sessions) repeated measures (baseline versus average post-treatment) analysis of variance.

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